REMARKS

Claims 1, 2, 4-7, 30-31, 38-39, 41-45, 47, and 112-118 were pending in the application. Claims 114 and 115 have been amended by the amendments presented herein. Accordingly, after the amendments presented herein have been entered, claims 1, 2, 4-7, 30-31, 38-39, 41-45, 47, and 112-118 will remain pending.

Specifically, support for the amendments to claims 114 and 115, can be found at, for example, page 10 lines 14-15, page 30 lines 13-14, and Examples 4 and 5.

No new matter has been added. Any cancellation of the claims should in no way be construed as an acquiescence to any of the Examiner's rejections and was done solely to expedite the prosecution of the application. Applicant reserves the right to pursue the claims as originally filed in this or a separate application(s).

Rejection of claims 1-2, 4-7, 30-31, 38-39, 41-47, and 112-113 under 103(a)

The Examiner has maintained the rejection of claims 1-2, 4-7, 30-31, 38-39, 41-47, and 112-118 under 35 USC 103(a) as being unpatentable over 5,859,312 ("Littman et al.") in view of Monbarts et al., McMurry et al., Rowen et al. and Rack et al.

Applicants traverse this rejection for the following reasons.

The Examiner maintains that the claimed invention is unpatentable over Littman et al. in view of Mombaert et al., McMurry et al, Rowen et al. and Rack et al. However, the cited references alone or in combination fail provide the requisite teachings of a non-human transgenic animal capable of producing heterologous T-cell receptors comprising unrearranged human T-cell receptor alpha and beta loci wherein said animal is capable of productive rearrangement of said human T-cell receptor α and β loci to encode functional heterologous T-cell receptors.

Regarding the teaching of McMurry et al, the Examiner indicates that Lauzurica and Krangel reference (1994. J. Exp. Med. 179: 43-55), cited by McMurry et al, stated that the mutated TCR minilocus was used "to serve as an innocuous reported that would not influence the rearrangement of endogenous TCR genes via the process of allelic exclusion". However, it is unclear which endogenous TCR genes would be affected by an unmutated construct as there is no evidence that productive rearrangement of one TCR delta allele inhibits rearrangement or

leads to allelic exclusion of the other TCR delta allele (see abstract of Sleckman et al. 1998. J. Exp. Med. 188: 1465-1471, provided previously). As such, Lauzurica and Krangel may have been concern that a human TCR delta minilocus construct capable of productive rearrangement could influence rearrangement of endogenous TCR genes through an "unnatural" allelic exclusion process.

The Examiner further alleges that McMurry et al. does not teach the expression of a rearranged human TCR would negatively influence thymic development. However, the second publication by Lauzurica and Krangel (1994. J. Exp. Med. 179: 1913-1921), also cited by McMurry et al., provides a second rationale for using the mutated TCR minilocus to "prevent a rearranged transgene from encoding a functional TCR protein and thereby influencing thymic development". While there is no further teaching in McMurry et al. or Lauzurica and Krangel as to what influence the transgenic TCR delta gene product would have on thymic development, there are many processes that take place in the thymus critical for the maturation and activation of functional T-cells (Godfrey & Zlotnick. 1993. Immunol. Today 14:547-553, provided previously). Taken together, a skilled artisan would understand that McMurry et al., by way of the teaching of the two Lauzurica and Krangel references, intentionally wish to avoid influencing allelic exclusion and thymic development by creating a nonfunctional human TCR delta minilocus. Thus, based on the teachings of McMurry et al., both of the cited Lauzurica and Krangel references and knowledge of the art at the time of the invention, a skilled artisan may expect that a transgenic human TCR locus capable of productive rearrangement and production of a functional TCR protein could affect TCR gene allelic exclusion and/or thymic development in a manner that would impact T-cell development, T-cell maturation and/or antigen stimulated T-cell responses.

The Examiner asserts that "the fact that Laruzurica and Krangel felt the need to mutate the V region genes in the human TCR δ transgene construct indicates that the authors expected that transgenic mice comprising the human TCR δ transgene would in fact productively rearrange this loci and express human TCR δ chains". However, it is clear that the McMurry et al. and the other cited publications expected that productive rearrangement of the human TCR δ locus would lead to changes in allelic exclusion and thymic development that could impact T-cell development, T-cell maturation and/or antigen stimulated T-cell responses. Thus McMurry

et al. teach away from a transgenic animals comprising human TCR α and β loci being capable of undergoing productive rearrangement wherein expression of heterologous TCR is necessary for T cell development, T cell maturation of antigen stimulated responses.

In a previous response (Jan. 29, 2007), Applicants provided details indicating that the α/β TCR loci and αβ T-cell developmental pathway differed significantly from the δ TCR minilocus and γδ T-cell developmental pathway taught by McMurry et al. The Applicants asserted that these differences would dissuade one skilled in the art from relying on the teachings of McMurry et al. in predicting successful generation of a transgenic animal comprising unrearranged human T-cell receptor α and β loci capable of productively rearranging the transgenic TCR loci and producing heterologous T-cell receptor. In the subsequent office actions, the Examiner changed the focus by stating that McMurry et al. taught that the TCR and immunoglobulin loci were similar in structure and that rearrangement of the TCR and Ig loci utilize the same recombination machinery. Based on these teachings and the state of the art of Ig transgenic animals provided in the prior art of record, the Examiner alleged that a skilled artisan would have a reasonable expectation of success that the presence of unrearranged TCR α and β loci in transgenic mice would lead to productive TCR rearrangement and expression of functional αβ TCR in T cells. In Applicants' last response (June 12, 2008), the Applicants acknowledged that McMurry et al describe some similarities between Ig and TCR loci; however, McMurry et al. also taught that there are multiple levels of cell type-specific and temporal regulatory controls that distinguish the productive rearrangement and functional expression of Ig and TCR molecules. Specifically McMurry et al. stated,

> Although the RSSs *(in reference to recombination signal sequences)* and the above-mentioned enzymatic activities *(in reference to RAG-1 and RAG-2 recombinases)* appear sufficient to direct the process of V(D)J recombination of extrachromosomal substrates, there is an additional level of developmental control exerted at endogenous antigen receptor loci (1, 2, 16, 30, 47, 52). For example, fibroblasts transfected with RAG-1 and RAG-2 fail to rearrange their endogenous Ig and TCR genes. Furthermore, developing B and T cells display tightly regulated rearrangement of individual antigen receptor loci. Fully rearranged TCR genes are formed only in developing T cells and fully rearranged Ig genes are formed only in developing B cells.
>
> McMurry et al. page 4553 column 2 (italics added for clarification)

McMurry et al. clearly teach that, despite the fact that the TCR and Ig loci are structurally similar and utilize the same recombination machinery, these common elements are insufficient to direct the process of recombination of the antigen receptor loci. Particularly, fibroblast containing unrearranged TCR loci and the appropriate recombination machinery are incapable of productive rearrangement and expression of functional TCR. McMurry et al. teach that there is some undefined "additional level of developmental control" required for productive rearrangement and expression of functional TCR. Moreover, there is nothing in the immunoglobulin transgenic mice literature of record to teach or suggest that similarities between TCR and Ig molecules would provide a reasonable expectation that mice carrying inactivated endogenous TCR loci and unrearranged heterologous TCR α and β loci should be capable of productive rearrangement of the TCR loci to encode functional heterologous TCRs. Thus, the teachings of McMurry et al. regarding "additional levels of developmental control" distinguishing T cell and B cell development are contrary to the statement that the TCR and Ig similarities (taught by McMurry et al.) and the state of the art of Ig transgenic mice would have led the skilled artisan to have a reasonable expectation of success that the presence of unrearranged TCR α and β loci in transgenic mice would lead to productive rearrangement and expression of functional $\alpha\beta$ TCR in T cells. Moreover, despite the similarities in the T cell and B cell developmental processes and the successful generation of human immunoglobulin transgenic mice, there is no teachings or suggestion in Littman et al. in view of Mombaert et al., McMurry et al., Rowen et al. and Rack et al. or the transgenic Ig mouse art of record that the unrearranged human α/β TCR loci, with their different sequence and structural properties from the immunoglobulin loci and murine α/β TCR loci, would be capable of replacing the murine TCR loci in transgenic mice resulting in productive rearrangement and expression of functional human TCRs to effect T-cell development, produce functional T-cells or elicit an effective antigen-stimulated responses.

Accordingly, for at least the above-identified reasons, Applicants believe that the instant claims are patentable over "Littman et al." in view of Monbarts et al., McMurry et al., Rowen et al. and Rack et al.

CONCLUSION

In view of the above amendment, applicant believes the pending application is in condition for allowance.

Dated: January 22, 2009

Respectfully submitted,

Electronic Signature: /Jonathan M. Sparks/
Jonathan M. Sparks, Ph.D.
Registration No.: 53,624
EDWARDS ANGELL PALMER & DODGE LLP
P.O. Box 55874
Boston, Massachusetts 02205
(617) 439-4444
Attorneys/Agents For Applicant